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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,713	10/22/2003	Timothy C. Thompson	PRO025/4-9CON2US	9759

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VINSON & ELKINS, L.L.P.
FIRST CITY TOWER
1001 FANNIN STREET, SUITE 2500
HOUSTON, TX 77002-6760

EXAMINER
YAO, LEI

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
01/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

cporter@velaw.com
IPTLdocket@velaw.com
bmelder@velaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/690,713	THOMPSON, TIMOTHY C.	
	Examiner	Art Unit	
	LEI YAO	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *33/5/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-31,33 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-31,33 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal brief filed on 11/9/2007, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options: (1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or, (2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37.

Claims 26-31, 33, and 35-39 are pending and under consideration for a method of treating prostate diseases with antibody to caveolin with or without androgen ablation therapy. .

All the rejections stated in the final office action dated 12/4/2007 are withdrawn in view of new ground(s) rejection in this office action.

Applicant's arguments in the Appeal Brief for the rejections based on the references in combination with respect to claims above have been considered but are moot in view of the new ground(s) of rejection below.

Claim Objection

Claims 27-29 are objected to under 37 CFR 1.75(c), as being of improper dependent form of previous claim. Applicant is required to cancel the claim(s), or

amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 26 is drawn to a prostate neoplastic disorder, wherein the disorder is metastasis. Claims 27-29 are further drawn to claim 26, wherein the disorder is displasia, hyperplasia, hypertrophy, or any benign prostatic disorder. One skilled in the art clearly know that the metastatic prostate cancer is late stages of a prostate cancer, while the prostate disorders listed above are the earlier stages of primary prostate cancer or pre-cancer conditions. Thus, claim 27-29 reciting these prostate disorder conditions are not within the scope of claim 26, which could not depend on claim 26 and do not further limit claim 26. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112**:**

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement:

Claims 26-29, 31, and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject having metastasis of prostatic neoplastic disorder comprising administering an anti-caveolin antibody, does not reasonably provide enablement for claimed method of treating other prostatic neoplastic disorder comprising displasia, hyperplasia, hypertrophy, or any

benign prostatic disorder listed in claims 27-29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to us the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims are drawn to a method of treating a subject having prostatic neoplastic disorders comprising benign prostatic conditions by administering the subject a composition comprising an anti-caveolin antibody. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. The objective of the claims is treating prostatic neoplastic disorder with antibody to caveolin, thus, it would be expected that one of skill in the art would be able to use claimed method to treat any prostate disorder including listed benign disorder with the antibody without undue a quantity of experimentations.

The specification teaches that metastases show higher levels of caveolin protein than primary tumors (table 1). The specification teaches increased apoptosis in antisense caveolin treated tumor. The specification further contemplates that both

malignant and nonmalignant disorders may be treated with claimed method. Non malignant disorders include displasia, hyperplasia, and hypertrophy. Examples of nonmalignant disorders include benign enlargement of the prostate, nodular hyperplasia, and benign prostatic hypertrophy.

One cannot extrapolate the teachings of the specification to the scope of the claims because the specification teaches metastases tumor expressing caveolin protein is high than the primary tumor, no showing or evidence on the levels of expressing such protein in benign prostate tumor or pre-cancer condition listed in the claim 27-29, and no direction/guideline or predictability is provided how or whether those benign tumors can be treated with anti-caveolin antibody.

The state of the art has clearly shown that the caveolin protein is overexpressed in the mammal metastatic cancer, which has suggested that reducing the caveolin levels may slow down the progression of malignant prostate tumor and benefit for prostate cancer treatment (Thompson, abstract, Cancer and Metastasis Review vol 17, page 439-442, 1999 and col 1, page 1876 of Yang et al Clinical Cancer Research vol 4, page 1873-80, 1998). In addition, Yang et al also teach primary and benign prostatic hyperplasic prostate samples having low or less caveolin staining (table 1-2 and page 1876, col 2, last paragraph). Thus, the state of the art has not shown a direct relation between the benign prostatic disorder and a high level of caveolin expression. Therefore, one skill in the art would not expect that any benign prostate disorder could be treated effectively with an antibody to caveolin.

Thus, in view of the contemporary knowledge in the art and the general lack of objective evidence in this applications for claimed method as well as the unpredictability in the art as discussed above, as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention as claimed.

Priority

Applicant's claims to earlier effective filing date 11/05/1997 through US provisional application 60064351 is acknowledged. However, upon review of the provisional application, it is noted that the application does not provide a support for claimed method of treating prostate neoplastic disorder comprising metastases with antibody to caveolin. Therefore, for the purposes of examining this application, the Office has established 11/05/1998 as effective filing date for examined claims. This date is the filing date of its parent application No.09186184.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 26, 30, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al (Clinical Cancer Research vol 4, page 1873-80, Aug, 1998. IDS: HHH) in view of Meredith et al (Prostate Carcinoma Radioimmunotherapy, vol 35 col 1017-1022, 1994).

Claims are drawn to a method for treating a subject having metastasis prostate cancer comprising administering to the subject a composition comprising an anti-caveolin antibody wherein the antibody is effective to inhibit metastasis in the neoplastic disorder wherein prostatic disorder is malignancy, hormone responsive, and prostate cancer, this include metastatic cancer.

Yang et al teach expression caveolin in the progressed prostate cancer (page 1873, col 1) and specifically teach that the mRNA and protein of caveolin are overexpressed in the metastatic prostate cancer and metastasis derived cell lines compared to the primary tumor samples (figure 1 and 2). Yang et al teach that immunohistochemical analysis shows minimal or barely detectable caveolin in normal prostate specimen and extensive accumulation in the metastatic prostate and lymph node metastasis specimen (page 1878, col 2, line 7-8 form bottom and 1879, tables 1-2).

Yang et al although do not specifically teach a method of using antibody to treat metastatic prostate cancer. Yang et al did suggest that the caveolin may be involved in or contribute to a pathway of metastatic cascade (page 1878, col 2), which suggests lowering the levels of caveolin could be benefit for treating a metastatic disease of prostate.

Treating metastatic tumor comprising prostate tumor with antibody specifically to the tumor antigen that contributes to the tumor metastases has been widely used currently in the art. For example, Meredith et al teach a method of treating metastatic prostate carcinoma with antibody to a tumor antigen, TAG-72, expressed in prostate carcinoma. Meredith et al teach that the antibody binding to the tumor antigen can localize to primary metastatic sites of prostate cancer and prevent bone metastases (entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the antibody to caveolin to treat metastatic cancer with expected result. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teaching of Yang et al with the teachings of Meredith et al in order to benefit the treatment for metastatic prostate cancer including hormone responsive tumor because Yang et al teach that caveolin is directly involved in process of prostate cancer metastasis that is hormone regulated. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teachings to treat metastasis of prostate cancer because Meredith et al has successfully treated metastatic prostate

cancer with antibody binding to a tumor antigen expressed by metastatic prostate cancer cells. Thus, the references in combination teach the limitation of the claims and the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

2. Claims 26, 30-31, 33, and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goethuys et al (Am J Clin Oncol. Vol 20, page 40-5, 1997) or Nasu et al (Nat Med, Vol 4, page 1062-3, September, 1998) in view of Yang et al (Clinical Cancer Research vol 4, page 1873-80, Aug, 1998. IDS-HHH), and Meredith et al (Prostate Carcinoma Radioimmunotherapy, vol 35 col 1017-1022, 1994).

Claims 26 and 30-31 are set forth above. Claims 35-39 are drawn to a method of treating a neoplastic disease of the prostate comprising administering to a subject in need thereof an anti-caveolin agent in conjunction with androgen ablation therapy, wherein the antibody is monoclonal or polyclonal antibody.

Since claims 26, 30-31 and 33 recite term “comprising administering”, and/or “hormone responsive” and since the prostate cancer are regulated with hormone androgen, the claims are included in this rejection.

Goethuys et al teach an association of prostate cancer with androgen and a standard method of treating prostate cancer with ablation of androgen. Goethuys et al teach and suggest combination therapy of androgen ablation with other therapy comprising immunotherapy.

Nasu et al teach that prostate cancers are often initially sensitive to androgen ablation and they eventually lose this response and continue to survive to became androgen independent (abstract). Nasu et al teach the relation between caveolin levels and androgen in the metastatic prostate cancer, that is, androgen-independent metastatic prostate cancer had increased caveolin levels and reducing caveolin expression increases the sensitivity of those prostate cell lines and metastatic prostate cancer to androgen (figures).

Goethuys et al or Nasu et al do not teach anti-caveolin antibody therapy for prostate cancer.

Yang et al specifically teach increase levels of caveolin protein in the progressed prostate cancer including a metastatic prostate cancer and metastasis derived cell lines compared to the normal prostate tissues as set forth above.

Meredith et al teach treating prostate cancer with antibody to a tumor antigen that is overexpressed on the prostate tumor cells as set forth above.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use an antibody to caveolin in conjunction with androgen ablation to treat progressed or metastatic prostate cancer with expected result. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of all the references in order to benefit the treatment for androgen dependent and independent prostate cancer because Goethuys et al has suggested immunotherapy is future of the treatment, Nasu teach that reducing the levels of caveolin could restore the sensitivity of metastatic prostate cancer to

androgen and Yang et al teach that caveolin is directly involved in process of prostate cancer metastasis that is hormone regulated. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teachings to treat metastasis of prostate cancer because Nasu have shown reducing caveolin levels with antisense nucleic acids to induce androgen sensitivity in the metastatic androgen-insensitive prostate cancer. Meredith et al has successfully treated prostate cancer with antibody binding to a tumor antigen expressed by metastatic prostate cancer cells. Thus, the references in combination teach the limitation of the claims and the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643